Original Research

# Utility of Tissue Doppler Imaging in Predicting Outcome in Patients with Idiopathic Pulmonary Fibrosis

Georgia Pitsiou[1], Christodoulos E. Papadopoulos[2], Haralambos I. Karvounis[2], Theodoros D. Karamitsos[2], Georgios Giannakoulas[2], Georgios Efthimiadis[2], Theodoros Kontakiotis[1], Paraskevi Argiropoulou[1], Georgios E. Parharidis[2]

*[1]Respiratory Failure Unit, Papanikolaou General Hospital, [2]1st Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece*

Key words: **Idiopathic pulmonary fibrosis, pulmonary hypertension, tissue Doppler imaging, survival.**

**Background:** There are limited reports in the literature concerning right ventricular (RV) performance in patients with non end-stage idiopathic pulmonary fibrosis (IPF) who exhibit mild to moderate pulmonary hypertension (PH). We evaluated RV functional impairment in such a cohort using both conventional echocardiography and tissue Doppler imaging (TDI) and in addition we assessed the association of specific TDI indices with survival.

**Methods:** Twenty-two clinically stable patients with non-end stage IPF and mild to moderate PH were assessed. Twenty-two healthy individuals served as controls. We evaluated RV systolic and diastolic function and further estimated peak pulmonary artery systolic pressure (PASP). In addition, by combining TDI and Doppler echocardiography, we calculated the ratio of trans-tricuspid E-wave velocity to early diastolic tricuspid annulus velocity (RV E/Em). Patients were followed for a median period of 22 months and the incidence of death was recorded.

**Results:** Both echocardiographic modalities revealed impaired RV systolic and diastolic function in the IPF group compared to controls. A significant negative correlation was observed between RV E/Em and PASP ($r=-0.5$, $p=0.018$). The probability of survival was 54.5% for those patients with RV E/Em $<4.7$ versus 100% for those with an index $>4.7$ (log-rank statistic 5.81, $p=0.016$).

**Conclusions:** TDI modality may serve as an alternative to conventional ultrasound technique for risk stratification and PH estimation in non end-stage IPF patients.

*Manuscript received:* January 11, 2007;
*Accepted:* March 12, 2007.

*Address:*
Christodoulos E. Papadopoulos

*95 Egnatias St.*
*54623 Thessaloniki,*
*Greece*
*e-mail:*
*chpapado@auth.gr*

Idiopathic pulmonary fibrosis (IPF) is characterised by progressive inflammatory and fibrotic processes of the lung, leading to pulmonary hypertension (PH) and resulting in severe morbidity and mortality due to respiratory failure.[1,2] A number of studies have evaluated the association of several factors with survival in patients with IPF, but there is still much controversy concerning their accuracy in the prediction of outcome. The severity of PH,[3] the timed walked test[4] and the distance-saturation product[5] during the 6 min walk test, resting pulmonary function,[6] a composite scoring system including clinical, radiographic and physiological variables[7] and many more have been associated with survival in IPF patients. Among these factors the severity of PH has been most widely investigated and stands as one of the most important surrogate markers of disease progression and outcome measurement.[3,8]

Pulmonary artery pressure estimation using Doppler echocardiography has almost replaced right heart catheterisation in the daily clinical routine practice of PH

assessment.[9] However, given the complex geometry and retrosternal position of the right ventricle (RV), and especially in advanced lung disease with the coexistence of lung hyperinflation, it is frequently difficult to make reliable measurements of the RV dimensions and function and to obtain an adequate tricuspid regurgitation signal for assessment of pulmonary artery pressure. On the other hand it is thought that in such populations systolic pulmonary artery pressure estimation by echocardiography is frequently inaccurate and may lead to over-diagnosis of PH.[9] Tissue Doppler imaging (TDI) echocardiography provides information about segmental myocardial motion and deformation during the cardiac cycle and is currently used to assess both systolic and diastolic function of both ventricles at a regional level.[10] Furthermore, it seems that this modality offers incremental prognostic information in patients with cardiovascular diseases and it is currently used for the risk stratification of these populations.[11-13]

To the best of our knowledge, no report at the present time has described RV regional myocardial involvement in a cohort of patients with non-end stage IPF characterised by mild to moderate PH. Accordingly, the objective of the present study was to assess the efficacy of TDI in the evaluation of RV function in such a population with lung hyperinflation and to compare this modality with the standard echocardiographic techniques in the detection of RV dysfunction. Finally we sought to evaluate the association of some specific TDI-derived indexes with PH and survival.

## Methods

Twenty-two patients (15 men, mean age 66 years; range 53 to 75 years) with IPF were studied. Diagnosis was based on American Thoracic Society/European Respiratory Society guidelines[14] and a clinical/high-resolution computed tomography (HRCT) diagnosis of fibrotic idiopathic interstitial pneumonia. The clinical criteria of the disease were as follows: a) exclusion of other known causes of interstitial lung disease; b) restrictive ventilatory defect or isolated reduction in gas transfer; c) age older than 50 years; d) insidious, unexplained dyspnoea on exertion; e) duration of illness greater than 3 months; and f) bibasilar inspiratory crackles.

For HRCT criteria, appearances compatible with fibrotic idiopathic interstitial pneumonia were required, as previously described.[15,16] HRCT abnormalities were predominantly basal/subpleural in distribution and comprised a mixture of reticular and ground glass abnormalities, with traction bronchiectasis when ground glass attenuation was prominent and no consolidation or nodules.

The mean time from initial diagnosis of the disease was 9 months. The patients were clinically stable and ambulatory at the time of the echocardiographic study and were recruited from outpatients attended by our unit over a period of 18 months. All subjects enrolled in the study had an adequate tricuspid valve regurgitation Doppler signal for assessment of pulmonary artery systolic pressure. Patients were determined to have non-end stage IPF and were categorised into 2 groups having none/mild versus moderate PH, according to a Doppler estimated mean pulmonary artery pressure gradient below 50 mmHg, and having no signs or history of *cor pulmonale*. Throughout the study they continued to receive the same medications, with steroids and/or azathioprine and acetylcysteine, while 5 of them were on $O_2$ therapy sufficient to maintain arterial saturation greater than 90%. Patients with a history of coronary artery disease, myocardial infarction, cardiomyopathy, valvular heart disease, symptoms or signs of RV failure, were excluded from further evaluation. Patients with atrial fibrillation and other rhythm abnormalities were also excluded from the study population. The control group consisted of 22 age- and sex-matched control subjects without any history of pulmonary and/or cardiac disease.

The protocol was approved by the Medical Ethical Committee of both Hospitals involved in the study and complied with the Declaration of Helsinki. All patients were informed about the aim of the study and the investigations to be performed and gave informed consent.

### *Pulmonary function studies*

All patients underwent spirometry (Transferrscreen II, Jaeger, Germany) within 1 week of the echocardiographic study. Dynamic and static lung volumes and single-breath carbon monoxide diffusing capacity were determined according to current guidelines.[17] Measurements of static lung volumes were made with the helium dilution method. All data are reported as a percentage of the predicted normal value. Arterial blood was taken with the patient sitting, breathing room air; pH, $pCO_2$ and $PO_2$ were measured with a blood gas analyser (ABL, Radiometer, Copenhagen). The functional capacity of subjects was quantitatively measured by performing the 6-min walk test, according to the current guidelines.[18] The test was administered by a single supervisor and standardised instructions

were given to each patient. The total distance walked and the initial and final oxygen saturation were recorded by finger pulse oximetry.

### Echocardiographic study

All patients and controls underwent a complete echocardiographic study, including two-dimensional, colour flow, spectral Doppler, as well as tissue Doppler Imaging using a GE Vingmed Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway). All images were saved digitally in raw-data format to magneto optical discs for offline analysis. Before each echo evaluation, brachial systolic and diastolic blood pressures were measured with the patient in a sitting position using a standard mercury sphygmomanometer.

Standard two-dimensional and colour flow Doppler images were obtained using the parasternal long and short axis and apical views. M-mode traces were recorded at a speed of 50 mm/s. Three consecutive cycles were averaged for every parameter. Resting left ventricular (LV) ejection fraction was obtained using the modified Simpson's biplane method. The RV end-diastolic diameter and RV free wall thickness were measured from the two-dimensional parasternal long axis view. RV end-systolic and end-diastolic areas were measured from the apical four-chamber view in order to calculate RV fractional area change.[19]

Pulmonary artery systolic pressure (PASP) was estimated by calculating the maximal velocity of the tricuspid regurgitant jet and by further using the Bernoulli equation and then adding to this value an estimated right atrial pressure based on both the size of the inferior *vena cava* and the change in diameter of this vessel during respiration.[20]

Pulsed Doppler echocardiography for the assessment of standard diastolic filling RV velocities was performed using the apical four-chamber view. Thus, the trans-tricuspid (RV) peak early filling velocity (E wave), peak late filling velocity (A wave), and their ratio (E/A) were obtained. All measurements were averaged from three end-expiratory cycles at a sweep speed of 100 mm/s, following current standards for the practice of echocardiography.[21]

Pulsed-wave TDI was used to assess tricuspid annulus velocities. Filters were set to exclude high-frequency signals, and the Nyquist limit was adjusted to a velocity range of 15 to 20 cm/s. Gains were minimised to allow for a clear tissue signal with minimum background noise. All TDI recordings were obtained during normal respiration. A 5 mm sample volume was placed in the apical four-chamber view on the lateral corner of the tricuspid annulus. Tricuspid (RV) annulus peak myocardial velocities during systole (Sm), early diastole (Em) and late diastole (Am) and their ratio (Em/Am) were recorded at a sweep speed of 100 mm/s. In addition, the ratio of early trans-tricuspid filling velocity (E wave) to early diastolic tricuspid annulus velocity (RV E/Em index) was calculated. Given the observation that this specific index when obtained for the LV was an accurate non-invasive correlate to LV filling pressure,[22] we sought to investigate the association between the RV E/Em index and PH severity.

From the pulsed tissue Doppler recordings time interval measurements were obtained using the internal analysis package of the ultrasound unit. Right ventricular ejection time (ET) was measured as the time from the onset to the end of the Sm wave on recordings from the tricuspid annulus. The RV isovolumic relaxation time (IVRT) was calculated from the end of the Sm wave to the beginning of the Em wave. The RV isovolumic contraction time (ICT) was measured from the end of the Am wave to the beginning of the Sm wave of the tricuspid annulus. Mean values were obtained by averaging three consecutive beats. The modified Tei index of global myocardial performance (MPI) obtained by the pulsed TDI was calculated as IVRT + ICT / ET for the RV.[23]

### Outcome measurement

Patients were followed for a median period of 22 months and the incidence of death was recorded, using telephone interview.

### Statistical analysis

The SPSS statistical software (SPSS, Inc., Chicago, Illinois, USA) was used. Data are expressed as mean ± SD and frequency expressed as a percentage. Differences between groups were assessed by Student's unpaired t-test. Categorical variables were compared using chi-square or Fisher's exact test, as appropriate. Linear regression analysis using Pearson's method was performed to assess univariate relations. In addition, stepwise multiple regression analysis was used to evaluate the effects of potential determinants on a dependent variable. To determine suitable cutoff points of RV E/Em, we constructed receiver operating characteristic curves to determine values in which sensitivity was as close as possible to specificity. The area under

the curve was measured to determine a summary measure of performance. Survival was plotted according to the Kaplan-Meier method, and mortality rates were compared using the log-rank test. A p-value $<0.05$ was considered significant.

### *Interobserver and intraobserver variability*

Intraobserver variability was established by having one observer measure echocardiographic data on at least two occasions in 10 subjects selected at random from the patient population under study (r=0.94). Interobserver variability was determined by having a second operator independently measure the same parameters in these subjects (r=0.89).

## Results

### *Characteristics of study population*

Of the total of 30 IPF patients evaluated and characterised as having non end-stage disease according to the methodology of the study, 22 were included in the study. Five patients were excluded because of an inadequate echocardiographic tricuspid regurgitation Doppler signal; one had mitral valve regurgitation, one a history of coronary artery disease and one atrial fibrillation.

Patients with IPF did not differ significantly in terms of sex, age, body mass index, smoking habits, baseline heart rate, blood pressure and LV systolic performance when compared to controls (Table 1). Table 1 also shows lung function parameters, resting gas exchange and the 6-min walk test data of IPF patients obtained according to the study methodology. Among IPF patients at the time of initial evaluation, 5 were on acetylcysteine therapy, 6 on azathioprine, 9 on prednisone and 5 on intermittent $O_2$ therapy. During the follow-up period 5 patients died, 4 due to respiratory failure decompensation and one following sepsis. No subjects were lost to follow up.

### *RV function assessment*

Two-dimensional echocardiography showed that IPF patients exhibited impaired RV function compared to controls. More specifically, they showed higher PASP values, worse RV systolic function, a more dilated RV chamber and more RV free wall hypertrophy (Table 2). Additionally, using standard Doppler echocardiography,

**Table 1.** Characteristics of the study population.

| | IPF patients (n=22) | Controls (n=22) |
|---|---|---|
| Male gender, % | 68.2 | 59.1 |
| Age, yrs | 65 ± 9 | 66 ± 6 |
| BMI | 27 ± 3 | 28 ± 4 |
| Ex-smokers, % | 23 | 32 |
| Non-smokers, % | 77 | 50 |
| Heart rate, bpm | 77 ± 8 | 70 ± 4 |
| Systolic BP, mmHg | 135 ± 8 | 138 ± 9 |
| Diastolic BP, mmHg | 88 ± 6 | 85 ± 7 |
| LVEF, % | 66 ± 5 | 70 ± 6 |
| Lung function parameters: | | |
| TLC, % predicted | 55.5 ± 14 | NA |
| FVC, % predicted | 62.3 ± 15 | NA |
| $FEV_1$, % predicted | 69.9 ±14 | NA |
| $FEV_1$/FVC, % | 89.8 ± 4 | NA |
| RV, % predicted | 53.1 ± 14 | NA |
| DLco, % predicted | 48.3 ± 18 | NA |
| Resting gas exchange: | | |
| $PaO_2$, mmHg | 63 ± 6 | NA |
| $PaCO_2$, mmHg | 38 ± 3 | NA |
| 6-min walk test: | | |
| Distance, m | 453 ± 120 | NA |
| $O_2$ desaturation, % | 7 ± 2 | NA |

BMI – body mass Index; LVEF – left ventricular ejection fraction; TLC – total lung capacity; FVC – forced vital capacity; $FEV_1$ – forced expiratory volume in 1 s; RV – residual volume; DLco – diffusing capacity for carbon monoxide; $PaO_2$ – arterial $O_2$ tension; $PaCO_2$ – arterial $CO_2$ tension; NA – non applicable.

**Table 2.** Echocardiographic assessment of right ventricular (RV) function in patients with idiopathic pulmonary fibrosis (IPF) and controls.

| | IPF patients (n=22) | Controls (n=22) | p value |
|---|---|---|---|
| Standard echocardiography: | | | |
| RVWT, cm | 0.56 ± 0.12 | 0.38 ± 0.15 | 0.001 |
| RVEDD, cm | 2.7 ± 0.3 | 2.3 ± 0.1 | <0.001 |
| RV area change, % | 42 ± 5 | 57 ± 6 | <0.001 |
| E/A | 0.7 ± 0.07 | 1.4 ± 0.1 | <0.001 |
| PASP, mmHg | 47 ± 12 | 24 ± 2 | <0.001 |
| Tissue Doppler imaging: | | | |
| Tricuspid annulus: | | | |
| Sm, cm/s | 15 ± 3 | 10.4 ± 1 | <0.001 |
| Em, cm/s | 9.6 ± 3 | 11 ± 2 | NS |
| Em/Am | 0.54 ± 0.1 | 1.5 ± 0.4 | <0.001 |
| E/Em | 5.7 ± 3 | 5.6 ± 1 | NS |
| ET, ms | 288 ± 49 | 315 ± 27 | 0.03 |
| IVRT, ms | 59 ± 15 | 49 ± 9 | <0.001 |
| MPI | 0.38 ± 0.08 | 0.28 ± 0.04 | <0.001 |

RVWT – RV free wall thickness; RVEDD – RV end-diastolic diameter; E/A – trans-tricuspid E to A wave ratio; PASP – pulmonary artery systolic pressure; Sm – peak systolic velocity; Em – peak early diastolic velocity; Em/Am – ratio of peak early to peak late diastolic velocity ratio; E/Em – ratio of E wave to peak early diastolic velocity; ET – RV ejection time; IVRT – RV isovolumic relaxation time; MPI – RV myocardial performance index.

we documented a characteristic reversal of the RV E/A ratio in IPF patients, indicative of diastolic dysfunction.

Surprisingly TDI analysis revealed a higher RV Sm in IPF patients compared to controls (Table 2). This finding indicates that in IPF patients with mild to moderate PH RV tricuspid annulus systolic velocity may not yet be impaired and the high values we observed might be the reflection of RV adaptation to the increased afterload. No significant differences were observed between the 2 groups concerning the RV Em and RV E/Em ratio. In contrast, a reversal of the RV Em/Am ratio was documented in the IPF group, similar to that obtained by Doppler echocardiography and indicative of a progressive greater contribution of late diastole to RV ventricular filling. Furthermore, IPF patients showed a more impaired MPI index when compared to controls, as a consequence of a shorter ET and a more prolonged IVRT (Table 2).

### *Association of PASP with specific indices*

We sought to investigate the association between PH severity, which represents a well studied risk factor in IPF patients, and several functional capacity parameters, lung function variables and TDI-derived echocardiographic indices of the study population.

Baseline spirometric measurements did not correlate with the severity of PH. In contrast, we found significant correlations between the PASP value and 6-min walked distance and various TDI derived indexes (Table 3). Of significant interest was the negative correlation between the RV E/Em index and PASP (r=-0.5, p=0.018, Table 3, Figure 1). By performing stepwise forward multiple linear regression analysis and using a p value <0.02 as the cutoff value needed for the inclusion of each specific factor in the multivariate analysis model, we found that the single most significant echocardiographic index for predicting PASP value was RV E/Em index (β coefficient: -0.536, p=0.01). Additionally, 6-min walking distance was revealed to be equally powerful (β coefficient: -0.528, p=0.01) for predicting PH severity (Table 4).

**Table 3.** Univariate relations between peak pulmonary artery systolic pressure and functional capacity parameters and echocardiographic indices of right ventricular function derived from tissue Doppler imaging.

| | r | p value |
|---|---|---|
| 6-min distance | -0.538 | 0.01 |
| Tricuspid annulus: | | |
| E/Em | -0.536 | 0.01 |
| MPI | 0.477 | 0.025 |
| Em/Am | -0.524 | 0.01 |
| Sm | 0.185 | 0.41 |

E/Em – ratio of E wave to peak early diastolic velocity; MPI – right ventricular myocardial performance index; Em/Am – ratio of peak early to peak late diastolic velocity ratio; Sm – peak systolic velocity.

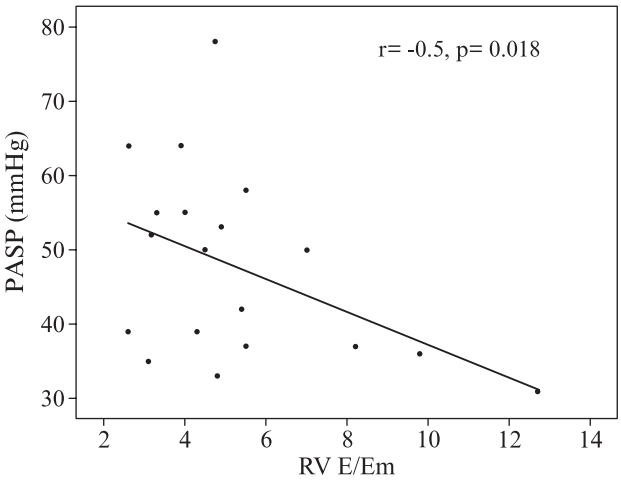


**Figure 1.** Scatter plot of Doppler-measured pulmonary artery systolic pressure (PASP) and ratio of early trans-tricuspid filling velocity to early diastolic tricuspid annulus velocity (RV E/Em) in patients with idiopathic pulmonary fibrosis.

**Table 4.** Predictors of peak pulmonary artery systolic pressure under multivariate analysis.

| | Univariate p | b-coefficient | p value |
|---|---|---|---|
| RV E/Em | 0.01 | -0.536 | 0.01 |
| 6-min distance | 0.01 | -0.528 | 0.01 |
| RV Em | 0.016 | ... | ... |

Em – tricuspid annulus peak early diastolic velocity; E/Em – ratio of E wave to tricuspid annulus peak early diastolic velocity.

## Survival analysis

Clinical follow-up of the original cohort was undertaken for a median period of 22 months. The receiver operating characteristic analysis indicated that an RV E/Em value of 4.7 was the best cutoff value for predicting outcome (Figure 2). This cutoff value was used to divide the cohort into 2 groups (Group 1, n=11, RV E/Em <4.7, and Group 2, n=11, RV E/Em >4.7). The probability of survival at the end of the follow up period was 54.5% for Group 1 versus 100% for Group 2 (log-rank statistic 5.81, p=0.016, Figure 3).

## Discussion

Idiopathic pulmonary fibrosis is a progressive fibrosing inflammatory lung disease characterised by a severe prognosis, with a mean length of survival after diagnosis ranging from 3 to 5 years.[25] To the best of our knowledge there are no studies in the literature evaluating

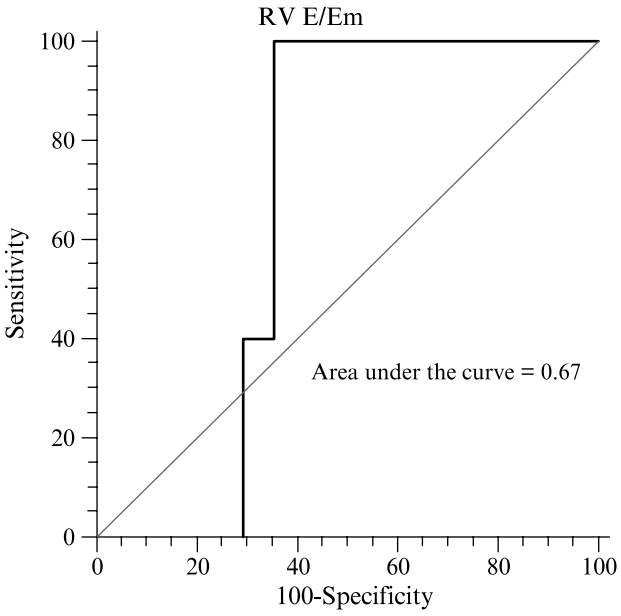


**Figure 2.** Receiver operating characteristic curve-derived cutoff value (ratio of early trans-tricuspid filling velocity to early diastolic tricuspid annulus velocity, RV E/Em = 4.7) predicting adverse outcomes in patients with idiopathic pulmonary fibrosis.

RV performance in patients with non end-stage IPF. It is therefore of great importance to investigate the way the RV adapts and performs in this clinical entity at a relatively early stage. In addition, it is crucial to find specific echocardiographic indexes for the early detection of the disease and for the risk stratification of these patients before severe PH is established. The present study underscores the usefulness of the TDI modality

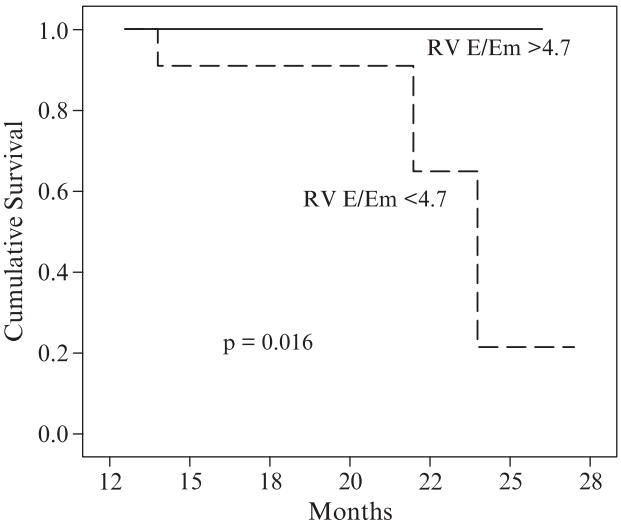


**Figure 3.** Cumulative survival in two groups of patients with idiopathic pulmonary fibrosis: those with ratio of early trans-tricuspid filling velocity to early diastolic tricuspid annulus velocity (RV E/Em) <4.7 and those with RV E/Em >4.7

as an alternative echocardiographic tool in assessing RV performance, in a cohort of clinically stable and ambulatory patients with IPF exhibiting mild to moderate PH and in whom no other cause of systolic and diastolic RV impairment was present. Furthermore, we demonstrated the incremental prognostic significance of the RV E/Em index, which was found to be strongly associated with the severity of PH, and we also determined that this specific index stands as an independent predictor of survival.

We detected RV systolic and diastolic function impairment in our cohort of patients and this finding was assessed by standard two-dimensional, Doppler and TDI echocardiography. More specifically, patients with IPF exhibited worse RV area change and had greater RV dimensions. Additionally, they showed a characteristic redistribution of RV filling to late diastole, indicative of diastolic dysfunction, and this finding was identical whether standard Doppler echocardiography or TDI was used. Furthermore, the evidence of disturbed MPI index compared to controls, as a consequence of a shortened ET and a prolonged IVRT, reinforce our observations of both systolic and diastolic function impairment in such a cohort.

Interestingly, RV Sm was greater in IPF patients than in controls and this finding could be attributed to RV adaptation to PH. This means that in patients with non end-stage disease, tricuspid annulus velocities remain unaffected and may exhibit values greater than normal, reflecting the hyperdynamic RV contraction that adapts to increased RV afterload.[25] Thus, we hypothesise that velocities fall later in the course of the disease, when PH becomes more severe and RV dilates, remodels, and *cor pulmonale* ensues. We would stress that the more hypertrophied RV free wall we observed in IPF patients partly supports the above hypothesis.

As far as we know, no other study has evaluated RV function in detail in a similar population of patients with mild to moderate PH secondary to IPF. However, there are some studies in the literature focusing on RV functional adaptation to diseases affecting the pulmonary circulation. Patients with systemic sclerosis,[26,27] systemic lupus erythematosus[28] and cystic fibrosis[29] have been assessed using the same modalities and were found to have similar characteristics, which in part support our results. The only highly significant difference observed was the value of RV Sm, which was found to be depressed in all 3 clinical entities when compared to controls. This obvious disagreement has been discussed previously and might be the expression of the diverse pathophysiology, the subsequent different RV functional adaptation in IPF, and could be mainly due to the fact that the vast majority of patients enrolled in these studies had severe PH.

A number of studies have documented the association between PH and outcome in diseases affecting RV performance, such as systemic sclerosis,[30] sarcoidosis[31] and chronic obstructive pulmonary disease.[32] Recently, Lettieri et al showed that PH is common in patients with IPF undergoing pre-transplantation right heart catheterisation and significantly impacts survival.[3]

We must stress that in patients with IPF the relationship of specific spirometric functional capacity indexes and PASP measurements with mortality has been the subject of some controversy.[4-7,33-35] This points up the need for further studies to evaluate the single most significant index for the risk stratification of such a population at a relative early stage. Accordingly, we evaluated the association of RV E/Em index with survival. We observed that when IPF patients had an RV E/Em index below 4.7 they faced a worse outcome when compared to patients with higher values. Furthermore, we found a statistically significant negative correlation between this index and PASP. These findings indicate that the association between RV E/Em and RV functional impairment in the population studied seems to be exactly the inverse of that observed when the relevant index is used for LV assessment and further prognosis.[11,12] The reason for that might be that the RV Em value in patients with mild to moderate PH is affected and reduced later in the course of the disease and, together with the increased RV Sm value, reflects the effective adaptation of RV to increased afterload, as discussed above. Thus, we conclude that the RV E/Em index is a significant predictor of mortality in patients with non-end stage IPF facing mild to moderate PH and that this easily accessible index could be routinely used for the risk stratification of such patients.

The findings of the present study may have some serious clinical implications. TDI-derived indexes for RV function obtained from the tricuspid annulus are usually easily measurable and show significant reproducibility, in contrast to some difficulties encountered even with TDI measurements of the RV free wall. Especially in those cases where the spectral profile of the tricuspid regurgitation jet is suboptimal, rendering PH estimation extremely difficult and increasing the need for right heart catheterisation, TDI may offer a significant alternative for the evaluation of PH severity, and perhaps for monitoring disease progression and assessing prognosis.

There are some limitations of this study that deserve comment. We included clinically stable and ambulatory patients who were referred to a single centre with suspected PH and all patients were evaluated to have mild to moderate PH. Thus, the results of the present study may not be extrapolated to the overall IPF population. Although the correlation between Doppler-estimated PASP and values measured by right heart catheterisation has been well documented, there seems to exist a greater variability among these values in patients with lung disease.[8] The evaluation of PH in this study by Doppler echocardiography and not by catheterisation, which stands as the gold standard method, could therefore be a limitation. However, the use of a TDI modality that showed significant correlations between some specific TDI-derived indexes and PH may render this limitation less significant. Another limitation of the present study could be the fact that tricuspid annulus TDI recordings could be influenced by the overall heart motion and the contraction of adjacent myocardial segments, rendering TDI less sensitive than strain rate imaging, which in addition is thought to be less load dependent.[36] Finally, length of survival was estimated from the time of patients' randomisation and not from the onset of symptoms. This fact, together with the relative small sample size, underscores the need for prospective studies evaluating this specific clinical entity.

### *Conclusions*

TDI represents an alternative modality to conventional echocardiography for the evaluation of RV performance in a cohort of clinically stable and ambulatory patients with non end-stage IPF. In this specific population TDI provides significant information that may be used to assess prognosis, estimate PH severity and possibly guide and monitor therapy.

## References


1. Noble PW, Homer RJ: Idiopathic pulmonary fibrosis: new insights into pathogenesis. Clin Chest Med 2004; 25: 749-758.
2. American Thoracic Society: Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646-664.
3. Lettieri CJ, Nathan SD, Barnett SD, et al: Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 129: 746-752.
4. Hallstrand TS, Boltano LJ, Johnson WC, et al: The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. Eur Respir J 2005; 25: 96-103.
5. Lettieri CJ, Nathan SD, Browning RF, et al: The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med 2006; 100: 1734-1741.
6. Erbes R, Schaberg T, Loddenkemper R: Lung function tests in patients with idiopathic pulmonary fibrosis. Are they helpful for predicting outcome? Chest 1997; 111: 51-57.
7. King TE Jr, Tooze JA, Schwarz MI, et al: Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. Am J Respir Crit Care Med 2001; 164: 1171-1181.
8. Nadrous HF, Pellikka PA, Krowka MJ, et al: Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. Chest 2005; 128: 2393-2399.
9. Arcasoy SM, Christie JD, Ferrari VA, et al: Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003; 167: 735-740.
10. Sutherland GR, Lange A, Palka P, et al: Does Doppler myocardial imaging give new insights or simply old information revisited (editorial). Heart 1996; 76: 197-199.
11. Hillis GS, Moller JE, Pellikka PA, et al: Noninvasive estimation of left ventricular filling pressure by e/e' is a powerful predictor of survival after acute myocardial infarction. J Am Coll Cardiol 2004; 43: 360-367.
12. Wang M, Yip GWK, Wang AYM, et al: Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003; 41: 820-826.
13. Meluzin J, Spinarova L, Hude P, et al: Prognostic importance of various echocardiographic right ventricular functional parameters in patients with symptomatic heart failure. J Am Soc Echocardiogr 2005; 18: 435-444.
14. American Thoracic Society / European Respiratory Society: International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2002; 165: 277-304.
15. Wells AU, Rubens MB, du Bois RM, et al: Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. AJR Am J Roentgenol 1993; 161: 1159-1165.
16. Wells AU, Hansell DM, Rubens MB, et al: The predictive value of appearances on thin section computed tomography in fibrosing alveolitis. Am Rev Respir Dis 1993; 148: 1076-1082.
17. American Thoracic Society: Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995; 152: 11107-11136.
18. American Thoracic Society statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166: 111-117.
19. Schiller NB: Two-dimensional echocardiographic determination of left ventricular volume, systolic function and mass. Summary and discussion of the 1989 recommendations of the American Society of Echocardiography. Circulation 1991; 83(Suppl): 1280-1287.
20. Schiller NB: Pulmonary artery pressure estimation by Doppler and two-dimensional echocardiography. Cardiol Clin 1990; 8: 277-287.
21. Appleton CP, Jensen JL, Hatle LK, et al: Doppler evaluation of left and right ventricular diastolic function: a technical guide for obtaining optimal flow velocity recordings. J Am Soc Echocardiogr 1997; 10: 271-292.
22. Ommen SR, Nishimura RA, Appleton CP, et al: Clinical util-

ity of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000; 102: 1788-1794.
23. Harada K, Tamura M, Toyono M, et al: Assessment of global left ventricular function by tissue Doppler imaging. Am J Cardiol 2001; 88: 927-932.
24. Panos RJ, Mortenson RL, Nicolli SA, et al: Clinical deterioration in patients with idiopathic pulmonary fibrosis: cause and assessment. Am J Med 1990; 8: 396-404.
25. Burghuber OC, Salzer-Muhar U, Gotz M: Right ventricular contractility is preserved in patients with cystic fibrosis and pulmonary artery hypertension. Scand J Gastroeneterol 1988; 143: 93-98.
26. Lindqvist P, Caidahl K, Neuman-Andersen G, et al: Disturbed right ventricular diastolic function in patients with systemic sclerosis: a Doppler tissue imaging study. Chest 2005; 128: 755-763.
27. D'Andrea A, Stisi S, Bellissimo S, et al: Early impairment of myocardial function in systemic sclerosis: Non-invasive assessment by Doppler myocardial and strain rate imaging. Eur J Echocardiography 2005; 6: 407-418.
28. Gin PL, Wang WC, Yang SH, et al: Right heart function in systemic lupus erythematosus: Insights from myocardial Doppler tissue imaging. J Am Soc Echocardiogr 2006; 19: 441-449.
29. Ionescu AA, Ionescu AA, Payne N, et al: Subclinical right ventricular dysfunction in cystic fibrosis. A study using tissue Doppler echocardiography. Am J Respir Crit Care Med 2001; 163: 1212-1218.
30. Lee P, Langevitz P, Alderdice CA, et al: Mortality in systemic sclerosis (scleroderma). Q J Med 1992; 82: 139-148.
31. Shorr AF, Davies DB, Nathan SD: Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 2003; 124: 922-928.
32. Oswald-Mammosser M, Weitzenblum E, Quoix E, et al: Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. Chest 1985; 107: 1193-1198.
33. Lederer DJ, Arcasoy SM, Wilt JS, et al: Six-minute walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006; 174: 659-664.
34. Harari S, Simonneau G, De Juli E, et al: Prognostic value of pulmonary hypertension in patients with chronic interstitial lung disease referred for lung or heart-lung transplantation. J Heart Lung Transplant 1997; 16: 460-463.
35. Timmer SJ, Karamzadeh AM, Yung GL, et al: Predicting survival of lung transplantation candidates with idiopathic interstitial pneumonia: does $PaO_2$ predict survival? Chest 2002; 122: 779-784.
36. Sutherland GR, Di Salvo G, Claus P, et al: Strain and strain rate imaging: a new clinical approach to quantifying regional myocardial function. J Am Soc Echocardiogr 2004; 17: 788-802.